2. RESPONSE/REMARKS

2.1 STATUS OF THE CLAIMS

Claims 1-7, 9-20, 23-33, 35, 36, 44, 46-48, 50, and 51 were pending at the time of the Action.

Claims 15, 33, 35, and 36 have been canceled herein without prejudice or disclaimer.

Claims 1, 14, 16-19, 23-24, 26, 29, 44, and 48 have been amended herein.

Claims 1-7, 9-14, 16-20, 23-32, 44, 46-48, 50, and 51 remain pending in the application.

2.2 SUPPORT FOR THE CLAIMS

Support for the pending claims can be found throughout the original claims, specification and figures as filed. It is Applicants' belief that no new matter is included as a result of the accompanying amendment.

2.3 SUBSTANCE OF INTERVIEW

A telephonic interview was conducted by the undersigned representative and Dr. James L. Grun on February 23, 2010. Applicants concur with the Interview Summary (FORM PTOL-413) issued by the Office on March 2, 2010 subsequent to the discussion with the Examiner. During the teleconference, the undersigned representative inquired about the content and format of a potential Rule 1.131 affidavit, which the Applicants may elect to submit, if any enablement and written description rejections remain of record following entry of the present amendment and consideration of the remarks and arguments presented herein.

Applicants appreciate Examiner Grun's willingness to consider such a submission, and his agreement in advance to conduct a second, and more detailed examiner interview with the undersigned representative upon the Office's receipt and consideration of the present submission.

2.4 THE REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, 1ST PARAGRAPH, IS OVERCOME.

Claims 14, 15, 17-19, 23-27, 33, and 35-36 were rejected under 35 U.S.C. § 112, first paragraph, allegedly as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims were also rejected under 35 U.S.C. § 112, first paragraph, allegedly as failing to enable one of skill in the art to which it pertains to make and/or use the invention commensurate in scope with these claims.

Claims 44, 46-48, 50, and 51 were rejected under 35 U.S.C. § 112, first paragraph, allegedly as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims were also rejected under 35 U.S.C. § 112, first paragraph, allegedly for failing to enable one of skill in the art to which it pertains to make and/or use the invention commensurate in scope with these claims.

As to each of these rejections, Applicants respectfully traverse. Initially, the standard is one of *ordinary* skill, rather than one *skilled* in the art, and the Office Action appears to have used a higher, more difficult to meet standard in connection with applicants' compliance with 35 U.S.C. § 112, first paragraph.

Further, the subject matter of amended claim 14 (and the claims that depend therefrom) is fully supported by the written description as filed. For example, as is described at the passage of the specification spanning pages 13 and 14:

> (t)he present inventors have now determined that a correlation exists between circulating NT- CNP, which has considerably higher concentrations than CNP in plasma, and skeletal growth. It has been noted by Tanner and Davies (2) that there is a progressive fall in skeletal growth rate from birth to pre-puberty. **The inventors have for the first time linked this steady state**

> **decline with a corresponding decline in circulating NT-CNP concentrations. Thus, the measurement of circulating NT-CNP lends itself as a marker of skeletal growth."** [Emphasis added]

These conclusions are based on the experimental data presented in the specification, and include the observations that: "(a)s shown in Figures 9A and 9B, there was a significant positive association in the 5-18 year age group between a marker of bone formation (ALP) and plasma NT-CNP($r = 0.55$, $p < 0.001$), and height velocity with plasma NT-CNP ($r = 0.57$, $p = 0.005$)." (*See, e.g.,* specification at page 34, last paragraph). Moreover, as noted on page 36 of the specification (2nd paragraph) "(t)he progressive fall of NT-CNP in lambs is consistent with the progressive reduction in cartilage tissue in long bones as the animal matures." Based on these experimental observations, the specification (bridging pages 27-28) described at the time of filing how NT-CNP could be used as "an index of future growth potential" and taught how such an assessment could be performed:

> From knowledge of the normal reference range (currently being compiled in children and maturing adults), indexed to known parameters (gender, chronological age, absolute height, bone age and growth velocity) — all themselves referenced to the growth curves of normal children — see Tanner *et al.* (2), the NT-CNP measurement provides the clinician with an objective assessment of the subject's future growth potential. Repeated measurements of NT-CNP in blood at specified intervals provide additional information on growth trends. This approach provides a means of monitoring and assessing efficacy of therapeutic interventions not otherwise available.
>
> By way of example, the point of finally attained (adult, fully mature) height in a subject could be determined by drawing a blood sample from a vein, separating the plasma and measuring the plasma NT-CNP concentration as described. Resultant NT-CNP levels would be compared with a representative sample of NT-CNP levels from mature adults. NT-CNP levels that fall within the reference range encompassing 95% of mature adults will indicate cessation of linear growth and make the use of drugs or other strategies for height promotion ineffectual. Repeat measurements, for example 3 months apart, showing similar mature adult levels would be confirmatory in doubtful cases. Plasma levels above the mature normal adult reference range would indicate significant growth plate activity remaining and therefore further potential for increase in height. These methods of estimating growth activity in children approaching full skeletal maturity are superior to other current methods such as "boneage" which is determined from the subjects left wrist

and takes no account of growth plates that actually contribute to increases in linear height.

In further support of the passage referenced in the application, Applicants have performed various studies to demonstrate that NT-CNP is predictive of growth potential. Examples of such data were previously submitted to the Office in the Declaration of Timothy Prickett, dated November 12, 2008, which accompanied the amendment and response filed November 24, 2008. For the convenience of the Examiner, Applicants attached hereto as **Exhibit A**, a portion of the relevant results.

In the particular study illustrated in **Exhibit A**, plasma NT-CNP and growth velocity were measured in 44 pre-adults over the course of 3-6 months. The results of that study are illustrated in Figure 1. As shown, growth cessation (defined as a growth velocity of less than 2 cm/year) was correctly predicted in 80% of subjects exhibiting a plasma NT-CNP less than 35 pmol/1. Overall NT-CNP has a sensitivity of 80% and a specificity of 86% in identifying growth potential and/or attainment of final adult height.

To that end, Applicants submit, therefore, that the subject matter of amended claim 14 is both enabled and supported by the written description of the application as filed, and as such, respectfully request that the rejection be withdrawn.

2.5 THE REJECTION OF CLAIM 27 UNDER 35 U.S.C. § 112, 2ND PARAGRAPH, IS OVERCOME.

Claim 27 was rejected under 35 U.S.C. § 112, 2nd paragraph, allegedly as being indefinite for filing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

Applicants respectfully traverse, and disagree with the Office's contention that Claim 27 is unclear. The diagnosis of a specific disease as described in the specification is made by comparing the NT-CNP level in the patient with a mean NT-CNP level of a sex- and aged-matched control population having one or more specific diseases/disorders. As would be appreciated by a worker of ordinary skill in the art, by comparison with such control "diseased" populations, an accurate diagnosis could be made. Thus, the claim is sufficiently definite, and as such, Applicants respectfully request that the rejection be withdrawn.

2.6 THE OBJECTION TO CLAIMS 1, 14-16, 29, 33, 36, 44, AND 48 IS OVERCOME.

Claims 1, 14-16, 29, 33, 36, 44, and 48 were objected to because of informalities. Applicants were requested to spell out the name indicated by the acronym "NT-CNP" at each first occurrence in the independent claims.

Applicants have amended the independent claims to recite "N-terminal pro-C-type natriuretic peptide (NT-CNP)" at its first occurrence. Applicants believe this fully addresses the Office's concern for claim clarity, and note that claims 1-7, 9-13, 16, 20, and 28-32 should now be in condition for allowance, as no other objections/rejections were entered against these claims.

Applicants respectfully request that the rejection now be withdrawn.

2.7 THE REJECTIONS OF CLAIMS 33, 35 AND 36 ARE RENDERED MOOT.

Claims 33 and 36 were rejected under 35 U.S.C. § 102(b), allegedly as being anticipated by Prickett* et al. *(*Biochem. Biophys. Res. Comm., *286:513, 2001).

Claims 33, 35, and 36 were rejected under 35 U.S.C. § 103(a), allegedly as being obvious over Prickett* et al. *in view of Buechler* et al. *(*U.S. Pat. Appl. Publ. No. 2003/0219734*).

Applicants respectfully traverse. Without acquiescing in any way with the propriety of these rejections, and solely in an effort to advance the remaining claims to ready allowance, however, Applicants have canceled claims 33, 35, and 36 without prejudice or disclaimer. The rejections therefore being moot, Applicants respectfully request that they now be withdrawn.

2.8 PROVISIONAL REQUEST FOR EXAMINER INTERVIEW

Pursuant to M.P.E.P. §§ 408, 713.01, and 713.09, and 37 C.F.R. § 1.133, should any issues remain in the mind of Examiner Grun, or should any claims remain rejected for any reason following entry of the present amendment and consideration of the remarks and response herein, Applicants respectfully request that the Office contact the undersigned representative to arrange an Examiner Interview at a mutually convenient time to discuss favorable disposition of the case and the resolution of any remaining issues of record.

Applicants provisionally make this request in order to facilitate an expeditious conclusion of prosecution on the merits in the above-captioned application, and to permit expedited allowance and issuance of the pending claims prior to the issuance of any subsequent action on the merits. Applicants appreciate in advance the Office's willingness to conduct such an interview, should any issues concerning patentability of the pending claims remain following entry of the present amendment and consideration of the response and remarks submitted herewith.

2.9 CONCLUSION

It is respectfully submitted that all claims are fully-enabled by the Specification, that all

pending claims are definite, and that the inventions embodied in those claims are useful, novel, and non-obvious. Applicants believe that the claims are acceptable under all sections of the Statutes and are now in condition for ready allowance. Applicants earnestly solicit concurrence by the Examiner and the issuance of a Notice of Allowance in the case with all due speed. Applicants note for the record their explicit right to re-file claims to one or more aspects of the invention as originally claimed in one or more continuing application(s) retaining the priority claim from the present and parent cases.

Should Examiner Grun have any questions, a telephone call to the undersigned Applicants' representative would be appreciated.

Respectfully submitted,

April 22, 2010
Date

Mark D. Moore, Ph.D. (Reg. No. 42,903)

HAYNES AND BOONE, LLP
Customer No. 27683
713-547-2040 Phone
214-200-0853 Fax

36697.17
H:833815v1

Certificate of Service

I hereby certify that this correspondence is being filed electronically with the U.S. Patent and Trademark Office *via* EFS-Web on April 22, 2010.

Michelle Baxter

Exhibit A

Use of Plasma NT-CNF as a predictor of skeletal growth potential.

Plasma NT-CNP concentration was measured in 44 pre adults as described in US 10/561,119. The growth velocity of these subjects was also measured in the subsequent 3-6 months. None of the subjects were receiving treatments known to inhibit linear growth . The predictive value of a plasma NT-CNP concentration in assessing growth potential was examined by receiver operator curve (ROC) analysis (see Fig 1 attached). Growth cessation (growth velocity less than 2 cms per year) was correctly predicted in 80% of subjects exhibiting a plasma NT-CNP less than 35 pmol/L. The area under the curve (AUC) was 0.90.

From these results, the applicant contends that measurement of NT-CNP in healthy pre adults has good predictive value (sensitivity 80%, specificity 86%) in identifying growth potential and/or attainment of final adult height, as would be appreciated by a skilled worker.

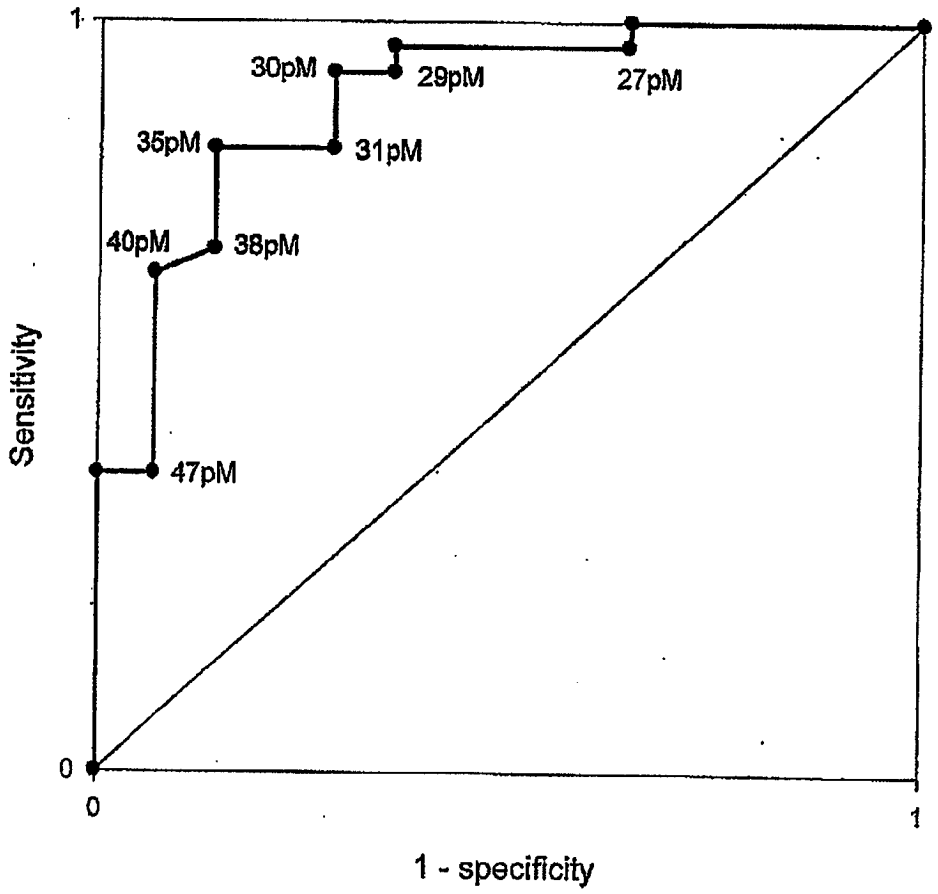

Figure 1

Figure 1 shows a receiver operator curve (ROC) for the different cut off values of plasma NT-CNP concentration used to predict cessation of linear growth in children and adolescents. Cessation of growth is defined as a growth velocity of less than 2 cm per year.